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Autism: a target of pharmacotherapies?

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Autism is reaching epidemic proportions. The diagnosis can be made as early as 2 years of age, and autistic patients are expected to have a normal life span. Thus, in terms of the number of 'patient years', autism spectrum disorder (ASD) represents a market that is as large as that of the biggest neurological indication, Alzheimer's disease. However, despite the clear unmet medical need no effective treatment is yet available. This could be because the biology of ASD is not clearly understood and thus proper drug treatment has not been possible. However, significant advances are being made toward understanding the mechanisms of the disease. Here, we review the most recent preclinical advances in the hope that they will lead to a breakthrough in the near future.

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▼ Autism is now recognized as a major problem with epidemic proportions [1,2]. The need for effective medical intervention is enormous. Here we review advances in autism research from a preclinical viewpoint with a focus on genetic and drug development aspects of the disease. Our goal is to draw attention to the need to do more research. First, we briefly describe what autism is and present the diagnostic criteria of the disease. Second, we make the argument that the prevalence of autism spectrum disorder (ASD) puts this disease on a par with the biggest neurological disorder, Alzheimer's disease (AD). Third, we describe numerous molecular culprits implicated in ASD and acknowledge that a clear pattern to the mechanisms of this disease has not emerged. However, we also argue that some of the molecular mechanisms identified might represent good pharmaceutical targets. Fourth, we discuss the currently employed drug therapies and state that they represent only palliative treatment and, finally, we delineate possible future preclinical research directions that might help us move forward in the analysis of the mechanisms of ASD.

Autism: a spectrum of developmental brain disorders that require clear diagnostic criteria

Autism is a developmental brain disorder characterized by abnormal social behavior, reduced interests in communicating and interacting with others, language disorders, repetitive and obsessive behaviors and rituals, and narrowly focused rigid interests (for review see [3]). Sensory overload and avoidance of novel stimuli is also typical in autism [4,5]. Not all of these symptoms are necessarily present in each patient, however, and the severity of the symptoms also varies among patients. Thus, perhaps one of the most fundamental problems in the treatment and research of autism is proper identification – or diagnosis. To address this issue, diagnostic instruments based on questionnaires and observation-based rating scales have been developed. The most well known of these include the Autism Diagnostic Interview, ADI [6] and its revision (ADI-R) [7], and the pre-linguistic Autism Diagnostic Observation Schedule, PL-ADOS [8] and its revised version (ADOS-G) [9]. These instruments evaluate three areas of autistic symptoms: social reciprocity, communication, and repetitive or restricted behaviors. However, the use of these diagnostic instruments is not yet widespread. This is unfortunate because well defined, detailed and standardized diagnostic tests should enable consistent rating of ASD patients, which would, first, enable the proper diagnosis of autism and thus aid the clinician and the parents/caregivers of autistic patients to employ appropriate therapeutic (pharmacological or environmental) intervention and, second, facilitate scientific analysis of this disease leading to the potential discovery of aspects of autism that might be influenced by different neurobiological mechanisms [3].

Autism was first described by Leo Kanner [10] and its less debilitating form, Asperger

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syndrome, by Hans Asperger (in ref [11]), diseases that are now are accepted to be different faces of the same disorder [11,12]. Today, four main categories are recognized on the ASD spectrum: (1) patients with known medical disorders, for example, tuberous sclerosis, exhibiting most of the typical signs of autism; (2) classic autism of the Kanner type [10,13]; (3) patients classified as having 'pervasive developmental disorders not otherwise specified' (PDD-NOS,) who have a milder form of autism or exhibit only subsets of the symptom cluster; (4) patients diagnosed as having Asperger syndrome [11,12] who have impaired social abilities but who possess normal, or occasionally superior, language skills and mental capacity.

Given the variable phenotypical characteristics of ASD and the potentially large number of genetic and environmental factors that might be involved in this disease, the development of treatment appears to be a formidable problem. This could explain why autism is often not in the portfolio of diseases that pharmaceutical and biotech research companies focus on. However, we also suspect that companies and academic institutes alike have paid little attention to this disease for another reason: they have underestimated the prevalence and the future impact of this disease.

Can we ignore autism as a disease affecting only a few unfortunate?

In the 1970s, autism was estimated to have affected ~1 in 5000 children. However, current prevalence estimates for ASD range from 1 in 500 children [14] to as high as 1 in 150 (see ref [2] and http://www.cdc.gov/ncbddd/dd/aic/about/default.htm). ASD is now regarded an 'epidemic' by the media [1] and by the scientific community [2]. Between 1980 and 2000 the number of publications on autism (registered by MEDLINE) quadrupled. In 1997, the NIH started a 5 year US$42 million network of collaborative programs on autism. A new center, the MIND (Medical Investigation of Neurodevelopmental Disorders) Institute at University of California at Davis (http://www.ucdmc.ucdavis.edu/mindinstitute/) solely devoted to the study of autism has recently opened. Recently, a Congressional (USA) caucus has been formed for autism.

In a recent report to the Legislature on the principal findings from the epidemiology of autism in California, the MIND Institute has found that the increase of incidence of ASD is real and can not be attributed to changes in diagnostic criteria or misclassification [15], although the generality of these results are debated. Funding for autism research has significantly increased: briefly, ASD represents an enormous market size. ASD can be diagnosed at 2 years of age [16], or even earlier (http://www.nichd.nih.gov/autism/CPEAupdate.htm) and autistic persons can live a normal lifespan [17]. The market size can thus be calculated as follows: $P_Y = P \times Y$; where P_Y is the number of 'patient-years', P is the number of patients and Y is the number of years for which patients live after diagnosis. Calculating with a recent prevalence estimate of 1 in 294 [18], there could be ~1 million ASD children in the USA alone, who could live for an average of 76 years. If diagnosed at age 2, PY can be calculated as follows: PY = 1000,000 × 74 = 74 million patient years.

To put this number into perspective, P_Y in the USA for AD, a disorder considered to represent the largest neurological disease market by many, is ~54 million (P = 9 million, as ~15% of people above 65 years in the USA will develop AD, and Y = 6, as AD patients live on average for 6 years after first diagnosis; see also Figure 1). The numerical estimate of patient years for ASD given here is a conservative

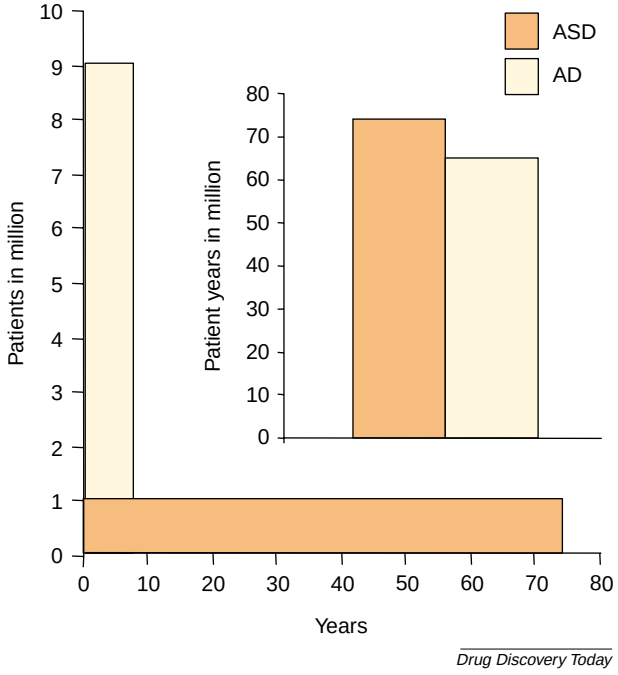

Figure 1. Autism spectrum disorder (ASD) is on par with Alzheimer's disease (AD), the biggest neurological disease market, in terms of market size. Market size is expressed as number of patient years. It is the area of the rectangles defined by the *x*-axis (number of years the patient suffers from the disease, i.e. the length of time for which the patient is expected to take medication) and the *y*-axis (number of patients suffering from the disease). The inset depicts the size of the area of the rectangles, and shows that the number of patient years, and thus the market size, is highly similar between ASD and AD. The estimate of patient years assumes that a patient will take the medication for the rest of their life. The number of ASD patients who might take the medication is based on the conservative estimate of 1 in 300 newborn.

estimate – it is likely to be higher in reality. Although it is probable that a developmental brain disorder like ASD will not be easily 'fixed' with a short drug treatment, whether patients will continue to use a drug throughout their life is, at present, speculative. Thus, the exact numbers characterizing the market size of ASD could change as we learn more about ASD and its pharmaceutical treatment options. Nevertheless, at this point it appears that ASD represents an unmet medical need that is comparable at least in order of magnitude to that of AD.

Mechanisms of the disease: is it the environment?

Perhaps one reason why autism is not among the major disease targets of pharmaceutical research is that the identification of molecular targets for which selective chemical compounds could be developed has been difficult and the targets discovered so far have been controversial. Briefly, the mechanism of ASD is not understood. Furthermore, it is still debated whether ASD is a predominantly unitary entity or a collection of phenotypes with multiple, varying etiologies. If the latter is true, it is likely to complicate the development of pharmacological intervention.

The increasing prevalence of ASD, if correct, could suggest environmental causes. One might argue that such an increase is unlikely to be due to genetic factors given that autistic patients rarely have children and parents with autistic children are also more likely to exercise birth control. Thus, natural selection should work against alleles of genes that could predispose patients to autism. Although this appears to be correct, the argument ignores the possibility of genotype–environment interactions as well as gene–gene interactions. That is, genes that predispose to autism could, under certain environmental circumstances and on certain genetic backgrounds, actually confer selective advantage and thus increase the frequency of autism in the population. At present, however, this possibility is purely speculative because neither the genetic nor the environmental causes of autism are clear. Although hotly debated, a large number of possible environmental causes have been implicated in autism, including injection of vaccines [19], exposure to toxins and infections [20], immunologic (autoimmune) problems [21] and metabolic problems [22,23]. Perhaps the most well known among these are the infection with German measles in pregnant mothers [24–26], the sedative drug thalidomide [27], the drug Pitocin, which is used to induce labor [28], and most recently synthetic compounds such as plastics and PCBs as well as some food additives [29; see also http://www.niehs.nih.gov/centers/res-core/ucd-res2.htm)]. However, the effects and mechanisms-of-action of these potential environmental insults are still hotly debated by both scientists and the public [1].

Finally, it must be noted that although evidence is mounting to suggest that autism is associated with abnormal development of brain structures leading to miswiring of the brain, the role of environmental stimulation, repeated practice of tasks and behavioral training [30–32] in the treatment of autistic persons can not be underestimated. This is because the brain is highly plastic and is expected to be able to make new synaptic connections and/or alter the strength of such connections throughout the entire life. This plasticity can be harnessed as argued by Rubenstein and Merzenich [33] and such (environmental) training therapies can be employed with success alone or perhaps in combination with drug treatment.

Mechanisms of the disease: are genes involved?

Although the environment clearly has a role, autism has been found to be one of the most heritable of human brain disorders. Even more importantly, several varieties of the autism spectrum have been found to run in families [34] raising the possibility that there might be a (set of) biological core mechanism(s) underlying the autism spectrum that are genetically tractable. If so, identification of the common underlying genes and their function might be possible and this should significantly advance the development of pharmacological intervention for a range of autistic patients.

Supporting the genetic argument, the concordance rate in monozygotic twins has been found to be 65%, whereas it is 0% in dizygotic twins [35], and the prevalence of autism has been found to be 100-times higher in families in which at least one autism case has been identified compared with the general population [36]. Based on such quantitative genetic findings it is believed that no more than 20 major genes underlie ASD [2]. If indeed there are only this few genes involved, the molecular and neurobiological mechanisms of autism might be easier to track than in psychiatric diseases like schizophrenia.

It was customary to pit the effects of the environment against the effects of genes and to argue which one is more or less important (the 'nature–nurture' debate). However, by now it has become clear that genes and the environment act in concert and influence the effects of one another. This is also likely in the case of ASD where certain genes might predispose the patient to the disease and might enhance or modify the effects of particular environmental insults. Although we disagree with genetic determinism, we propose that genetic analysis will enable the discovery of important molecular components underlying

ASD and thus will facilitate the unraveling of its neurobiological mechanisms. For example, although the number of familial (heritable) cases in another disease, AD, is only a tiny fraction (4–5%) of the total number of cases, identification of the genetic culprits (e.g. the amyloid precursor protein or the presenilins) in these familial cases has made an invaluable contribution to our understanding of the neurobiological mechanism of AD in general.

Candidate loci: genes potentially associated with ASD in the human population

Population studies enable the linkage or association between autistic traits and genetic markers to be revealed. Such studies implicated several candidate loci or chromosomal regions in ASD [37]. For example, the long arm of chromosome 7 (e.g. the 7q31 region, the $SPCH_1$ locus, the *CAGH44* gene [38,39], the $5HT_{2A}$ locus and serotonin in general [40–42], the Wnt_2 gene [43] and the Reelin locus [44]) have been identified as possible loci of interest. Chromosomal abnormalities involving the 15q11–13 region and a segment of 13q have also been suggested. Unfortunately, however, some of these findings are yet to be replicated and several are debated.

Single gene mutations have also been identified in patients with autism. The rare tuberous sclerosis complex (TSC) is due to dominant mutations of two functionally related genes, *TSC1* and *TSC2* [45,46]. The rate of autism in TSC patients is high (17–68%) but the rate of TSC patients among autistic persons is only 3%, indicating that TSC is not the main underlying mechanism in autism. Nevertheless, a relatively rare genetic alteration can be a valuable tool with which molecular mechanisms of a disease can be untangled. Fragile X syndrome (caused by the expansion of a polymorphic CGG repeat upstream of the coding region of the *FMR1* gene leading to blockade of gene expression [47]) has also been implicated in autism because some fragile X patients exhibit autistic symptoms [48]. As in TSC, fragile X might illuminate some possible mechanisms that contribute to autism.

Of high importance is the fact that autism is 4–5 times more prevalent among males [5]. The mechanism of this gender bias is not known but recently two X-linked genes encoding neuroligins NLGN3 and NLGN4 have been found to be associated with autism [49]. Neuroligins are thought to interact with neurexins and influence synaptic development and function. Arx, the first transcription factor implicated in autism [50], is also X-linked. The gender bias, however, does not necessarily mean sex chromosome linkage; it could be due to any autosomal genes including those whose expression is modulated by sex hormones.

Neurotransmitter systems: could an imbalance of excitation and inhibition be the explanation?

Three main neurotransmitter systems have been implicated in autism, the serotonergic system, the glutamatergic system, and the GABAergic system. GABA receptors are involved in inhibitory neurotransmission and influence both developmental and functional plasticity of the brain. A cluster of GABA receptors are localized to the Prader-Willi/Angelman locus on 15q11–13 [51], a region found to be trisomic in some autistic patients and considered a likely susceptibility locus [52]. Also, an autoradiographic study showed reduced binding of ^{3}H-flunitrazepam and ^{3}H-muscimol (benzodiazepine binding sites on $GABA_A$ receptor) in the hippocampus of autistic patients [53]. With regard to the serotonergic system, increased blood [40] and urine [54] serotonin levels have been detected in autistic patients and, paradoxically, serotonin reuptake inhibitors that are believed to increase serotonergic tone have been found to ameliorate some symptoms of autism [55]. The reduced functioning of the glutamate system has also been proposed in ASD [56]. Glutamate is the most abundant neurotransmitter in the brain and by binding to a large number of ionotropic (ion channel) and metabotropic (G-protein coupled) receptors it is responsible for excitatory synaptic transmission.

Numerous compounds have been developed that can modulate the function of certain glutamate receptors. However, efficacy has not been evaluated for most of them with regard to autism. Perhaps the best studied of these compounds are the AMPAkines, or AMPA potentiators. These compounds could increase glutamatergic 'tone' in autistic patients because they can potentiate the effect of glutamate specifically at the AMPA-R – this is an ionotropic glutamate receptor, a ligand gated calcium channel that is expressed abundantly throughout the brain and is involved in a large number of cellular and synaptic processes including long-term potentiation (LTP). Clinical trials of these compounds specifically aimed at autism have been initiated (Cortex Pharmaceuticals; http://www.cortex-pharm.com). Linkage and association between the gene encoding GluR6, another ionotropic glutamate receptor, and autism has also been identified [57] but compounds for this target have not been investigated for autism.

In an attempt to reconcile the complex molecular picture and the fact that there are several quantitatively and qualitatively different forms of autism not one of which is clearly associated with a particular molecular target, Rubenstein and Merzenich [33] suggested a model in which they propose that the common element in autism is an increase of excitation to the expense of inhibition in key neural systems that results from either genetic or epigenetic

Table 1. Examples of molecular mechanisms suspected in autism spectrum disorder (ASD)

Molecular mechanism, gene or chromosomal region	Relevance for ASD	Refs
SPCH1 gene	Autosomal dominant language disorder	[39]
CAGH44 gene	Mutation detected in speech and language disordered patient	[38]
5HT2A gene	Linkage studies and serotonergic hypothesis	[40,41]
Wn*t*2 gene	Linkage studies and animal model showing signs similar to autism	[43]
Reelin gene	Reduced expression in autistic patients	[44]
15q11-13 & 13q chromosomal regions (potentially numerous genes)	Linkage and association studies	[73]
GABA receptors	Reduced expression in autistic patients	[53,47]
TSC1 and *TSC2* genes	Prevalence of ASD is high among persons carrying mutant TSC alleles	[45,46]
FMR1 gene	ASD-like symptoms in Fragile-X patients	[48]
ADSL gene	Point mutation in family exhibiting autistic features	[58]
ADA allele 2	Increased frequency in autistic patients	[59,60]
Oxytocin, Vasopressin genes	Function in social behavior, blood levels reduced in ASD, animal model with social behavior disturbance	[61–63,75]
BDNF gene	Expression elevated in ASD children	[64]
En2 gene	Association studies, known role in cerebellar development	[76–78]
X-chromosome (potentially numerous genes, e.g. neuroligins and Arx)	Significantly higher incidence of ASD in males versus females (4:1 ratio). X chromosome appears protective.	[5,50]

The list is not exclusive and is continuously growing.

factors. According to this argument, combinations of genes and/or environmental insults might lead to autistic symptoms and not one single factor is responsible for the development of the abnormalities. If this model is correct, drugs that reduce neural excitation (e.g. several glutamate receptor antagonists or inverse agonists) or increase inhibition (e.g. GABA-R agonists) could be efficacious in autism, a suggestion that might be gaining some support in recent analysis of the effects of benzodiazepines (acting through GABA receptors) and anticonvulsants (often expected to act through glutamate receptors) in autistic patients (reviewed in [33]).

Beside the major neurotransmitter systems, other possible mechanisms have been suggested. These involve, for example, adenylosuccinate lyase (ADSL) [58], adenosine deaminase (ADA) [59,60], neuropeptides oxytocin and vasopression [61–63], brain derived neurotrophic factor (BDNF) [64] and perhaps an array of other genes whose expression might be altered in autism [65].

As previously implied, several molecular candidates implicated in ASD are typical drug targets. Neurotransmitter receptors, including receptors of GABA, glutamate, 5HT or neuropeptides fall into this category. Other targets, such as BDNF and its tyrosine kinase receptor, have also been considered in drug development. The Wnt signaling pathway has been extensively studied and might yield components that represent druggable targets. In summary, a large number of potential molecular mechanisms have been discovered (Table 1) but at this point it is unclear which of these might represent the drug targets whose pharmaceutical modulation could ameliorate the core symptoms of autism. In addition, a large number of animal models (including genetic and drug based models) have been proposed (Table 2) but their use in drug development and the analysis of the mechanism of ASD is still debated.

Appropriate drug treatment has yet to be found

Unfortunately, despite the clear unmet medical need and the large number of potential molecular targets, no suitable drug treatment is available for autistic patients. A lack of more suitable alternatives before the proper diagnostic criteria for ASD, led to the widespread use of antipsychotic

Table 2. Examples of animal models of autism spectrum disorder (ASD)

Model	Target molecule or function/area	Phenotypical alteration	Refs
Eker Rat (spontaneous mutation)	TSC2		[79]
TSC2 transgenic mouse (introduced mutation)	TSC2		[80]
Fragile X mouse (null mutant)	FMR1 mutation	Subtle learning deficits	[81–84]
En2 KO mouse (null mutant)	En2	Subtle cerebellar abnormalities, motor learning impairment	[78,85]
Vasopressin deficient rat (spontaneous mutation)	Vasopressin	Reduced social memory and other learning deficits	[86]
Dvl1 KO mouse (null mutant)	Dvl1 and Wnt signaling pathway	Impaired social behavior and sensorimotor gating	[87]
Reelin mutant mouse (spontaneous mutation)	Reelin	Cytoarchitectural abnormalities similar to those of ASD, but severe ataxia	[88]
Oxytocin KO mouse (null mutant)	Oxytocin	Deficits in ocial behavior	[75]
GS Guinea Pig (spontaneous mutation)	Unknown	Abnormal exploratory behavior, sleep, hypopholiation of vermis, reduced number of cerebellar Purkinje cells	[89]
Bachevalier's Rhesus Monkey (experimental lesion)	Amygdala	Abnormal social behavior (only transient)	[90]
Rat cerebellar model (experimental lesion)	Vermis	Hyperactivity, increased perseveration, reduced attention	[91]
Rat amygdala model (experimental lesion)	Amygdala	Abnormal social behavior	[92]
Valproic acid toxicity in rat (experimental drug injection)	Embryonic brain development	Structural abnormalities in vermis	[93]
Borna virus rat model (experimental virus delivery)	Post natal brain development	Cerebellar abnormalities, reduced play behavior	[94]
Zebra fish development	Brain development	Numerous potential developmental alterations	[95]

Both genetic (induced or spontaneous mutation) and non-genetic (e.g. lesion or drug manipulation) models are listed. Note that not all models have been evaluated for potential phenotypical (behavioral) alterations.

drugs in autistic patients. Haloperidol, pimozide and fluphenazine have been reported to have some ameliorative effects (for review see [55]) but these drugs are currently avoided because of their significant side effects. Clozapine and olanzapine have also been tried with limited or no success (reviewed in [55]). Risperidone has been investigated the most in recent studies and it has been found to treat moderate to severe behavioral problems that are associated with autism [66]. Risperidone is similar to clozapine in that it has a similarly complex pharmacological profile. It is chemically unrelated to any other currently available antipsychotic drugs and is a potent $5HT_{2A}$, $5HT_7$, α_1-, α_2-adrenergic, and histamine H_1 antagonist. It also acts as a weak antagonist at the D_2 dopamine receptor. Risperidone treatment [55,66] has been reported to improve sensorimotor functioning, effectual reactions, reduce repetitive behaviors, irritability and aggression, and improve the overall behavioral symptoms score. Impairments in social interaction and the use of language, however, remained unaltered in response to risperidone treatment. Buspirone, a partial agonist at the $5HT_{1A}$ autoreceptor has also been reported to reduce aggression, hyperactivity, and repetitive behaviors [55]. The opioid antagonist naltrexone has been theorized to be beneficial [55] because

it might reduce the effect of endogenous opioids and thus lead to reduction of self-absorbed 'introvert' attitude. However, clinical trials have shown that this drug has no, or a very mild, effect.

Based on observations suggesting hyperserotonemia, it might seem reasonable that drugs enhancing synaptic levels of 5-HT, such as selective serototonin reuptake inhibitors (SSRIs) would worsen autistic symptoms. However, fluoxetine (Prozac), an SSRI that has been widely prescribed for depression indication, was found to ameliorate symptoms including repetitive, compulsive and aggressive behaviors. Children on Prozac also tended to sleep better, make better eye contact, and retain more flexibility in their behavior (reviewed in [55]).

Secretin is a newly proposed treatment that has been in the spotlight of the lay public, the popular media and the scientific community [22]. Secretins belong to a family of enterohormones that are involved in both the function of the gastrointestinal tract and the CNS [22]. Secretin receptors have been found in the cerebellum, and a secretin-like polypeptide has been found in several brain regions. Furthermore, secretin has been reported to lower plasma 5-HT levels. Developed from a chance observation, secretin has now been the subject of double-blind, placebo-controlled studies. Uunfortunately, these trials have not shown efficacy compared to placebo (reviewed in [67]). In summary, despite the large number of drugs tried, present drug therapy is only palliative at best.

Future directions

Given the heterogeneity of the manifestation and of the mechanisms of ASD, further development of detailed diagnostic criteria and testing/evaluation methods that will enable classification of ASD phenotypes and clustering of symptom sets are needed [68]. They will help both therapists and basic research scientists. Identification of autistic features in the population might also facilitate drug development as the need for such drugs in milder forms of ASD will be better appreciated. It is also noteworthy that some of the features of ASD can be observed in other CNS disorders, including schizophrenia, nonverbal learning disorders, communication disorders and attention deficit hyperactivity disorders [5]. Thus, drugs developed for ASD might ameliorate symptoms associated with these diseases, and vice versa, and help a larger number of patients than what has been estimated based on the prevalence of ASD, an important consideration for market analysis.

Because a significant proportion of ASD cases are of heritable type it should be possible to identify genetic markers that could be tested early. Early diagnostic markers would aid the development and implementation of intervention strategies. Early intervention is considered to be crucial because the best results have been achieved when the behavioral modification or training is started at the youngest possible age [30–33].

Identification of the molecular targets with the use of linkage analysis or with DNA microarrays [65,69] is crucial for modeling the disease and for development of compounds that interact with the targets. Identification of druggable targets, however, might also be facilitated by bioinformatics tools [70]. These tools will enable us to navigate the often sketchy or at best complex web of mechanisms implicated in ASD and lead to the discovery of potentially unexpected biochemical steps and unforeseen druggable targets.

Finally, although numerous behavioral tests have been used in preclinical drug development, no test battery has been developed that would specifically and consistently measure the main aspects of autistic-like features in animals. Some attempts have been made to fill this need ([71] and references therein). Development of test batteries for intra-specific social behaviors, social interaction, communication, social learning, while keeping the ethological characteristics of the species in mind [72] will be a step forward because such tests will aid the proper characterization of drug effects in preclinical research.

In summary, autism research has a lot of problems to solve but the rate with which discoveries are being made is accelerating, and with the combined efforts of neurobehavioral geneticists, pharmacologists, bioinformaticists and psychologists, it is hoped that proper treatments for this disorder will soon be discovered.

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